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grounds of rejection that are not necessitated by amendment, and therefore should not have been made Final.

In the Office Action, claims 71-73 are rejected under 35 U.S.C. §112, first paragraph, for alleged lack of enablement. Claims 1, 4-12, 18-21, 27-29, 35-38, 44-49, 54, 57-61, 77-79, 88, 89 and 94-99 are rejected under 35 U.S.C. §102(e) as allegedly being anticipated by Hochrainer *et al.* (U.S. Patent No. 6,150,418). Claims 13-17, 22-26, 30-34, 39-43, 50-53, 55, 56, 58, 65-67, 71-73, 80-87, 92, 93 and 97-99 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Hochrainer *et al.*

The rejection under 35 U.S.C. §112, first paragraph, is made for this first time in the Office Action. Hochrainer *et al.* is cited for the first time in the Office Action.

It is stated in the Office Action that Applicant's amendment necessitated the new grounds of rejection. Applicant respectfully traverses this finding for the following reasons.

The instant Office Action is the second action on the merits in this application. The first Office Action on the merits was mailed May 22, 2002. In a response mailed August 22, 2002, Applicant amended only claim 8 to correct an obvious typographical error as follows:

8. (Amended) The pharmaceutical composition of claim 7, wherein the tonicity adjusting agent is ammonium carbonate, ammonium chloride, ammonium lactate, ammonium nitrate, ammonium phosphate, ammonium sulfate, ascorbic acid, bismuth sodium tartrate, boric acid, calcium chloride, calcium disodium edetate, calcium gluconate, calcium lactate, citric acid, dextrose, diethanolamine, dimethylsulfoxide, edetate disodium, edetate trisodium monohydrate, fluorescein sodium, fructose, galactose, glycerin, lactic acid, lactose, magnesium chloride, magnesium sulfate, mannitol, polyethylene glycol, potassium acetate, potassium chlorate, potassium chloride, potassium iodide, potassium nitrate, potassium phosphate, potassium sulfate, [propylene] propylene glycol, silver nitrate, sodium acetate, sodium bicarbonate, sodium biphosphate, sodium bisulfite, sodium borate, sodium bromide, sodium cacodylate,

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sodium carbonate, sodium chloride, sodium citrate, sodium iodide, sodium lactate, sodium metabisulfite, sodium nitrate, sodium nitrite, sodium phosphate, sodium propionate, sodium succinate, sodium sulfate, sodium sulfite, sodium tartrate, sodium thiosulfate, sorbitol, sucrose, tartaric acid, triethanolamine, urea, urethan, uridine or zinc sulfate.

No other claims were amended and no new claims were added.

Accordingly, it is respectfully submitted that the amendments of the claims do not necessitate the new grounds of rejection. To the extent that the amended claims could be rejected over the new reference and on the new grounds, the original claims could have been so-rejected, since the claims prior to the first Office Action on the merits and the claims as amended in response thereto are substantively identical.

Because the present Office Action raises issues that could have been raised in the first Office Action on the merits, and entry of an Amendment After Final is discretionary with the Examiner, applicant may be denied the opportunity to address these issues.

In light of the above remarks, reconsideration of the finality of the Office Action is respectfully requested.

CLAIM 92

The Office Action states that claims 1-61, 65-67, 71-73, 77-89 and 93-99 are pending herein. Applicant respectfully submits that claim 92 has not been cancelled and is pending in the instant application. Appropriate correction is respectfully requested.

REJECTION OF CLAIMS 71-73 UNDER 35 U.S.C. §112, FIRST PARAGRAPH

Claims 71-73 are rejected under 35 U.S.C. §112, first paragraph, for alleged lack of enablement. The Office Action alleges that the specification does not contain any data showing the instantly claimed composition will, in fact, prevent or ameliorate one or more symptoms of diseases or disorders

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associated with undesired and/or uncontrolled bronchoconstriction. Applicant respectfully traverses this rejection.

Relevant Law

In order to satisfy the enablement requirement of 35 U.S.C. § 112, first paragraph, the specification must teach one of skill in the art to make and use the invention. *Atlas Powder Co. v. E.I. DuPont de Nemours*, 750 F.2d 1569, 224 USPQ 409. That some experimentation is needed, does not preclude enablement as long such experimentation is not undue. *In re Marzocchi et al.*, 469 USPQ 367 (CCPA 1971). The requirements of 35 USC § 112, first paragraph can be fulfilled by the use of illustrative examples or by broad terminology. *In re Anderson*, 176 USPQ 331, 333 (CCPA 1973):

...we do not regard section 112, first paragraph, as requiring a specific example of everything within the scope of a broad claim What the Patent Office is here apparently attempting is to limit all claims to the specific examples, notwithstanding the disclosure of a broader invention. This it may not do.

The amount of experimentation that is permissible depends upon a number of factors, which include: the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability of the art, and the breadth of the claims. *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Int'f 1986); see also *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988).

The instant claims

Instant claim 71 is directed to an article of manufacture containing packaging material, an aqueous composition containing the composition of claim 1 formulated for single dosage administration, which is useful for treatment, prevention or amelioration of one or more symptoms of diseases or disorders associated with undesired and/or uncontrolled bronchoconstriction, and a label

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that indicates that the composition is used for treatment, prevention or amelioration of one or more symptoms of diseases or disorders associated with undesired and/or uncontrolled bronchoconstriction.

Claim 72 is directed to a similar article of manufacture containing the composition of claim 53. Claim 73 is directed to a similar article of manufacture, containing the composition of claim 58.

Argument

The specification adequately teaches one of skill in the art to make and use the compounds and practice the claimed methods without undue experimentation

The amount of direction or guidance presented

The specification provides numerous patents and publications establishing that formoterol compositions are useful in the treatment, prevention, or amelioration of one or more symptoms of diseases or disorders associated with undesired and/or uncontrolled bronchoconstriction. See, *e.g.*, page 12, line 3 to page 13, line 22:

To date, formoterol has been formulated as a dry powder and administered via devices such as the Turbuhaler® and the Aerolizer®. See, *e.g.*, Seberova *et al.* (2000) *Respir. Med.* 94(6):607-611; Lotvall *et al.* (1999) *Can. Respir. J.* 6(5):412-416; Campbell *et al.* (1999) *Respir. Med.* 93(4):236-244; Nightingale *et al.* (1999) *Am. J. Respir. Crit. Care Med.* 159(6):1786-1790; Lecaillon *et al.* (1999) *Eur. J. Clin. Pharmacol.* 55(2):131-138; Bartow *et al.* (1998) *Drugs* 55(2):303-322; Ekstrom *et al.* (1998) *Respir. Med.* 92(8):1040-1045; Ringdal *et al.* (1998) *Respir. Med.* 92(8):1017-1021; Totterman *et al.* (1998) *Eur. Respir. J.* 12(3):573-579; Palmqvist *et al.* (1997) *Eur. Respir. J.* 10(11):2484-2489; Nielsen *et al.* (1997) *Eur. Respir. J.* 10(9):2105-2109; Ullman *et al.* (1996) *Allergy* 51(10):745-748; Selroos *et al.* (1996) *Clin. Immunother.* 6:273-299; and Schreurs *et al.* (1996) *Eur. Respir. J.* 9(8):1678-1683.

Formoterol is also available as a tablet and a dry syrup in certain areas of the world (*e.g.*, Atock®, marketed by Yamanouchi Pharmaceutical Co. Ltd., Japan). Formoterol formulations are also available in other areas (*e.g.*, Europe and U.S.) for propellant-based metered dose inhalers and dry powder inhalers (*e.g.*, Turbuhaler®,

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Aerolizer® and Foradil Aerolizer®). None of these formulations are water based. Sterile, stable, aqueous based inhalation solutions of formoterol for nebulization are not available, nor have they been reported.

Compositions containing formoterol in combination with other active ingredients have been disclosed. See, e.g., U.S. Patent Nos. 6,004,537, 5,972,919 and 5,674,860 (formoterol and budesonide), 5,668,110, 5,683,983, 5,677,280 and 5,654,276 (formoterol and IL-5 inhibitors), 6,136,603 (formoterol and antisense modulators of IL-5), 5,602,110 (formoterol and millrinone), 5,525,623 (formoterol and a tryptase inhibitor), 5,691,336, 5,877,191, 5,929,094, 5,750,549 and 5,780,467 (formoterol and a tachykinin receptor antagonist); and International Patent Application Publication Nos. WO 99/00134 (formoterol and rofleponide) and WO 99/36095 (formoterol and a dopamine D₂ receptor agonist).

Other compositions containing formoterol have been disclosed in U.S. Patent Nos. 5,677,809, 6,126,919, 5,733,526, 6,071,971, 6,068,833, 5,795,564, 6,040,344, 6,041,777, 5,874,481, 5,965,622 and 6,161,536.

U.S. Patent No. 6,150,418 discloses a "liquid active substance concentrate" containing formoterol in the form of its free base or in the form of one of the pharmacologically acceptable salts or addition products (adducts) thereof as active substance. This "liquid active substance concentrate" is reported to be a concentrated (i.e., greater than 10 mg/mL, preferably 75 to 500 mg/mL) solution or suspension that is stable for a period of several months possibly up to several years without any deterioration in the pharmaceutical quality. This patent teaches that it is the high concentration that allows for the stability of the concentrate. The "liquid active substance concentrate" is not suitable for direct administration to a patient.

U.S. Patent No. 6,040,344 discloses an aqueous aerosol formulation of formoterol tartrate for use in a nebulizer. This patent states that the formulation disclosed therein is not attractive for long term storage.

Such patents and publications, all of record herein, provide extensive evidence that one of skill in the art would expect that the compositions contained in the articles of manufacture of instant claims 71-73 would be expected to be useful in treatment, prevention, or amelioration of one or more symptoms of diseases or disorders associated with undesired and/or uncontrolled bronchoconstriction. For example, as described in the quoted text

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of the specification, a dry powder formulation of formoterol (Foradil®) is marketed in the U.S. for treatment of asthma and prevention of bronchospasm (see, *e.g.*, Doctor's Guide to Medical and Other News:

<http://www.docguide.com/dg.nsf/PrintPrint/51->

B076796B49F922852569F50070BD1C, and Products F-H from the Novartis website: http://www.novartis.com/products/en/product_list_fh.shtml).

Relative skill of those in the art

In this instance, the level of skill in the art is high. This is evidenced by the art in this area, which is authored primarily by those with Ph.D. and M.D. degrees and is intended for an audience of similarly highly skilled individuals.

Breadth of the claims

Claims 71-73 are dependent claims that are directed to articles of manufacture containing the compositions of claim 1, 53 and 58, respectively. These compositions are all stable, aqueous compositions of formoterol for administration by nebulization. Formoterol is known to be useful in the treatment, prevention, or amelioration of one or more symptoms of diseases or disorders associated with undesired and/or uncontrolled bronchoconstriction (*supra*). Therefore, claims 71-73 are not unduly broad and are enabled by the disclosure of the specification.

Compliance with the USPTO Guidelines

The USPTO has released "Guidelines for Examination of Applications for Compliance with the Utility Requirement" [guidelines, which address utility under 35 U.S.C. §101 and 35 U.S.C. §112, first paragraph] and an "Overview of Legal Precedent Governing the Utility Requirement" [legal overview] to support the guidelines. Under section I.B.4. of these guidelines Examiners are reminded that:

they must treat as true credible statements made by an applicant or a declarant in the specification or in a declaration provided under 37 CFR

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§1.132, unless they can show that one of ordinary skill in the art would have a rational basis to doubt the truth of such statements.

Further, the legal overview provided by the USPTO, in section II.B.1., explains that:

[a]n applicant's assertion of utility creates a presumption of utility that will be sufficient, in most cases to satisfy the utility requirement of 35 U.S.C. §101. To overcome this presumption, *the Examiner must establish that it is more likely than not that one of ordinary skill in the art would doubt the truth of the statement of utility.* In other words, the Examiner must show that the asserted utility is not credible. [Emphasis added; see e.g., *In re Langer* 503 F. 2d 1380, 183 USPQ 288 (CCPA 1974)].

The legal overview goes on to explain, in section II.B.2., when an asserted utility is not "credible":

To assess credibility, the Examiner should determine if one of ordinary skill in the art would consider the assertions of the applicant to have any reasonable scientific basis. If they do, they should not be challenged as not being credible. Only where they do not [*e.g.*, if the assertion is "incredible in view of contemporary knowledge"], should the Examiner challenge the statement as not being credible.

Thus, the Examiner must accept as true any credible statement of utility made by the Appellant and may only challenge the statement upon a showing that those of skill in the art would consider the assertion *to have no reasonable scientific basis.*

Further, there is no requirement that the utility of a pharmacologically active substance be proven by *in vivo* testing. *In re Isaacs*, 146 USPQ 193, 195 (CCPA 1965). *In vitro* tests can raise the presumption of *in vivo* utility of the claimed compounds. "A standard *in vitro* test may be sufficient to demonstrate pharmacological activity of a compound." *Bigham v. Godtfredsen*, 222 USPQ 632, 637 (Bd. Pat. App. & Int'f. 1984), see, also *Nelson v. Bowler*, 206 USPQ 881, 883 (CCPA 1980); and *Cross v. Iizuka*, 224 USPQ 739, 741 (Fed. Cir. 1985). With respect to pharmacological and therapeutic utilities, the

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legal overview provided by the USPTO, in section I.C., interprets *Nelson v. Bowler* as establishing the following:

Knowledge of the pharmacological activity of any compound is *obviously beneficial to the public*. It is inherently faster and easier to combat illnesses and alleviate symptoms when the medical profession is armed with an arsenal of chemicals having known pharmacological activities. *Since it is crucial to provide researchers with an incentive to disclose pharmacological activities in as many compounds as possible, we conclude that adequate proof of any such activity constitutes a showing of practical utility. These general principles are equally applicable to situations where an applicant has claimed a process for treating a human or animal disorder. [Emphasis added.]*

The legal overview addresses the analysis of "credibility" of such utilities, in section II.B.2., as follows:

"Special care should be taken when assessing the credibility of an asserted therapeutic utility for a claimed invention. In such cases, *a previous lack of success* in treating a disease or condition, *or the absence of a proven animal model* for testing the effectiveness of drugs for treating a disorder in humans, *should not, standing alone, serve as a basis for challenging the asserted utility under §101.*" (Emphasis added)

Finally, the USPTO, in its legal overview, addresses some special considerations regarding asserted therapeutic or pharmacological utilities [Section III.] stating:

"The Federal courts have consistently reversed rejections by the Office asserting a lack of utility under §101 for inventions claiming a pharmacological or therapeutic utility where an applicant has provided evidence supporting such a utility. In view of this, Examiners should be particularly careful in their review of evidence provided in support of an asserted therapeutic or pharmacological utility."

Thus, where a credible pharmacological utility is asserted by an applicant, it must be assumed by the Examiner to be a true statement of utility unless the Examiner shows that one of skill in the art would find no rational scientific basis for the asserted utility.

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In *In re Brana* 34 USPQ2d 1436, U.S. App. LEXIS 6362 (Fed. Cir. 1995)
the Court has stated:

[A] specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirement of the first paragraph of §112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. *In re Marzocchi*, 58 C.C.P.A. 1069, 439 F.2d 220, 223, 169 U.S.P.Q. (BNA) 367, 369 (WP 1971).

From this it follows that the PTO has the initial burden of challenging a presumptively correct assertion of utility in the disclosure. *Id.* at 224; 169 U.S.P.Q. (BNA) at 370. Only after the PTO provides evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility does the burden shift to the applicant to provide rebuttal evidence sufficient to convince such a person of the invention's asserted utility. See < = 21 > *In re Bundy*, 642 F.2d 430, 433, 209 U.S.P.Q. (BNA) 48, 51 (WP 1981). n17.

The PTO has not met this initial burden. The references cited by the Board, Pazdur and Martin, n18 do not question the usefulness of any compound as an antitumor agent or provide any other evidence to cause one of skill in the art to question the asserted utility of applicants' compounds. Rather, these references merely discuss the therapeutic predictive value of *in vivo* murine tests -- relevant only if applicants must prove the ultimate value in humans of their asserted utility. Likewise, we do not find that the nature of applicants' invention alone would cause one of skill in the art to reasonably doubt the asserted usefulness. . . .

Taking these facts -- the nature of the invention and the PTO's proffered evidence -- into consideration we conclude that one skilled in the art would be without basis to reasonably doubt applicants' asserted utility on its face. The PTO thus has not satisfied its initial burden. Accordingly, applicants should not have been required to substantiate their presumptively correct disclosure to avoid a rejection under the first paragraph of § 112. *In re Marzocchi*, 439 F.2d at 224, 169 U.S.P.Q. (BNA) at 370.

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In this instance, the publications and patents cited in the application demonstrate that the compositions, which contain formoterol, contained in the articles of manufacture of instant claims 71-73 have activity in the treatment, prevention, or amelioration of one or more symptoms of diseases or disorders associated with undesired and/or uncontrolled bronchoconstriction. No credible reasons to doubt the asserted utility have been set forth.

Therefore, since the claims encompass articles of manufacture that contain compositions that have the asserted utility (activity), there is no reason to doubt the asserted utility. Thus, the requirements of 35 U.S.C. §112, first paragraph, have been satisfied.

REJECTION OF CLAIMS 1, 4-12, 18-21, 27-29, 35-38, 44-49, 54, 57-61, 77-79, 88, 89 AND 94-99 UNDER 35 U.S.C. §102(e)

Claims 1, 4-12, 18-21, 27-29, 35-38, 44-49, 54, 57-61, 77-79, 88, 89 and 94-99 are rejected under 35 U.S.C. §102(e) as allegedly being anticipated by Hochrainer *et al.* (U.S. Patent No. 6,150,418). Applicant respectfully traverses this rejection.

The relevant law

Anticipation requires the disclosure in a single prior art reference of each element of the claim under consideration. *In re Spada*, 15 USPQ2d 1655 (Fed. Cir., 1990), *In re Bond*, 15 USPQ 1566 (Fed. Cir., 1990), *Soundsciber Corp. v. U.S.*, 360 F.2d 954, 148 USPQ 298, 301, adopted 149 USPQ 640 (Ct. Cl., 1966). See, also, *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 USPQ2d 1913,1920 (Fed. Cir.), *cert. denied*, 110 S.Ct. 154 (1989). "[A]ll limitations in the claims must be found in the reference, since the claims measure the invention". *In re Lang*, 644 F.2d 856, 862, 209 USPQ 288, 293 (CCPA, 1981). Moreover, it is incumbent on the Examiner to identify wherein each and every facet of the claimed invention is disclosed in the reference. *Lindemann Maschinen-fabrik GmbH v. American Hoist and Derrick Co.*, 730 F.2d

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1452, 221 USPQ 481 (Fed. Cir., 1984). Further, the reference must describe the invention as claimed sufficiently to have placed a person of ordinary skill in the art in possession of the invention. An inherent property has to flow naturally from what is taught in a reference. *In re Oelrich*, 666 F.2d 578, 581, 212 USPQ 323, 326 (CCPA, 1981). "Rejections under 35 U.S.C. §102 are proper only when the claimed subject matter *is* identically disclosed or described in the "'prior art'" "...the [r]eference must clearly and unequivocally disclose the claimed compound or direct those skilled in the art to the compound without *any* need for picking, choosing, and combining various disclosures not directly related to each other by the teachings in the cited references. Such picking and choosing may be entirely proper when making a rejection of a 103, obviousness rejection, where the applicant must be afforded an opportunity to rebut with objective evidence any inference of obviousness which may arise from the *similarity* of the subject matter which he claims to the prior art, but it has no place in the making of a 102, anticipation rejection." [Emphasis in original]. *In re Arkey, Eardly, and Long*, 455 F.2d 586, 172 USPQ 524 (CCPA, 1972).

The instant claims

As amended herein, claim 1 is directed to a pharmaceutical composition, containing formoterol, or a derivative thereof, in a pharmacologically suitable fluid, wherein the composition is stable during long term storage, the fluid contains water, and the composition is formulated at a concentration suitable for direct administration to a subject in need thereof.

Claims 4-12, 18-21, 27-29, 35-38, 44-49, 54, 57-60 77-79, 88, 89 and 94-99 further describe the composition of claim 1. Claim 61 is directed to a nebulized solution containing formoterol or a derivative thereof in a pharmacologically suitable fluid.

The disclosure of Hochrainer *et al.*

"Active Substance Concentrate"

Hochrainer *et al.* discloses an "active substance concentrate" containing formoterol in the form of its free base or in the form of one of the pharmacologically acceptable salts or addition products (adducts) thereof as the active substance. This "active substance concentrate" is taught as a "highly concentrated" solution or suspension (*i.e.*, greater than 10 mg/mL, preferably 75 to 500 mg/mL) that is stable for a period of several months, possibly up to several years without any deterioration in the pharmaceutical quality (see, *e.g.*, column 1, lines 55-61; column 2, lines 4-7; and claim 1).

Hochrainer *et al.* discloses that it is the high concentration that allows for the stability of the concentrate. The cited reference does not disclose stable, aqueous compositions containing formoterol formulated at a concentration for direct administration to a subject in need thereof, as required by the instantly-claimed compositions.

The "highly concentrated" "active substance concentrate" of the reference is not suitable for direct administration to a subject in need thereof. See, *e.g.*, column 2, lines 1-4:

The term "highly concentrated" means a concentration of the active substance which is usually too high to enable the corresponding solution or suspension to be used therapeutically for inhalation without being diluted.

See also, *e.g.*, column 1, lines 47-52:

The active substance concentrate according to the invention may be converted, by diluting with a pharmacologically acceptable liquid which optionally contains pharmaceutical adjuvants and additives, into a pharmaceutical preparation (aerosol formulation) which is converted by means of a nebulizer into an inhalable aerosol.

See also, *e.g.*, column 4, lines 9-13:

The active substance concentrate according to the invention is not usually suitable as such for direct medicinal use, particularly for inhalation. As already explained, use of the active substance concentrate comprises converting it into a pharmaceutical preparation (aerosol formulation).

Thus, the "active substance concentrate" of Hochrainer *et al.* is merely a means for the storage of highly concentrated solutions of formoterol, and is not formulated at a concentration for direct administration to a subject in need thereof.

"Pharmaceutical Preparation"

Hochrainer *et al.* discloses that the "active substance concentrate" is converted to a "pharmaceutical preparation" prior to administration to a patient. See, *e.g.*, column 1, lines 47-53 and columns 4-5. The reference does not disclose that the "pharmaceutical preparation" is stable during long term storage. As described in detail below, the reference discloses that such formoterol compositions are not stable during long term storage.

The "pharmaceutical preparation" of Hochrainer *et al.* is disclosed for administration to a patient. See, *e.g.*, column 4, lines 13-18:

The term "pharmaceutical preparation" denotes a formulation of a pharmaceutical substance suitable for inhalation wherein a pharmaceutical substance or mixture of substances can be administered in the required and/or recommended concentration.

The reference also discloses methods for administration of the "pharmaceutical preparation" to a patient in need thereof (see, *e.g.*, columns 4-5). However, the reference does not disclose that the "pharmaceutical preparation" is stable during long term storage.

Hochrainer *et al.* further distinguishes the "active substance concentrate" disclosed therein from a "pharmaceutical preparation" at column 5, lines 16-19:

Neither the active substance concentrate suitable for storage according to the invention nor the pharmaceutical preparation for administration obtained by dilution contains a propellant.

Differences from the instant claims

Hochrainer *et al.* discloses a highly concentrated solution or suspension of formoterol "active substance concentrate" that is suitable for storage, but is not suitable for direct administration to a subject in need thereof. The reference discloses that the formoterol "active substance concentrate" is converted to a "pharmaceutical preparation" which is administered to a patient. The reference does not disclose that the "pharmaceutical preparation" is stable during long term storage.

In contrast, the instantly-claimed pharmaceutical compositions containing formoterol are formulated in a pharmacologically suitable fluid, where the composition is stable during long term storage, the fluid contains water, and the composition is formulated at a concentration suitable for direct administration to a subject in need thereof. Hochrainer *et al.* does not disclose these compositions.

Hochrainer *et al.* discloses an "active substance concentrate" that must be diluted prior to administration to a subject in need thereof. The reference does not disclose that the "pharmaceutical preparation" resulting from dilution of the "active substance concentrate" is stable during long term storage. To the contrary, the reference discloses that:

In the past it has been found that liquid aerosol formulations of formoterol are not suitable for use in inhalers intended for ambulatory inhalation treatment since *formoterol cannot be stored in a sufficiently stable manner in solution to guarantee the pharmaceutical quality of the formulation over lengthy periods of time.* (emphasis added)

See, column 1, lines 30-35 of the reference. Therefore, based on the disclosure of Hochrainer *et al.*, one would expect that the "pharmaceutical preparation" is not stable during long term storage.

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Therefore, instant claims 1, 4-12, 18-21, 27-29, 35-38, 44-49, 54, 57-61, 77-79, 88, 89 and 94-99 are not anticipated by the disclosure of Hochrainer *et al.*

REJECTION OF CLAIMS 13-17, 22-26, 30-34, 39-43, 50-53, 55, 56, 58, 65-67, 71-73, 80-87, 92, 93 and 97-99 UNDER 35 U.S.C. §103(a)

Claims 13-17, 22-26, 30-34, 39-43, 50-53, 55, 56, 58, 65-67, 71-73, 80-87, 92, 93 and 97-99 are rejected under 35 U.S.C. §103(a) as allegedly being obvious over Hochrainer *et al.* (U.S. Patent No. 6,150,418). The Office Action alleges that the determination of the concentrations of buffer, formoterol and anticholinergic agents recited in the rejected claims is within the level of skill of one of ordinary skill in the art and that one of ordinary skill in the art would have been motivated to determine such concentrations to achieve the maximum effect of the recited components. Applicant respectfully traverses this rejection.

The relevant law

[I]n order to establish a *prima facie* case of obviousness, there must be evidence, preferably a teaching, suggestion, incentive or inference from the cited art or in the form of generally available knowledge that one of ordinary skill would have been led to modify the relevant teaching to arrive at what is claimed. *In re Papesch*, 315 F.2d 381, 391, 137 USPQ 43, 51 (CCPA 1963).

The prior art must provide a motivation whereby one of ordinary skill in the art would have been led to do that which the applicant has done. *Stratoflex Inc. v Aeroquip Corp.*, 713 F.2d 1530, 1535, 218 USPQ 871, 876 (Fed. Cir. 1983). In addition, the mere fact that the prior art may be modified in the manner suggested by the Examiner does not make the modification obvious unless the prior art suggests the desirability of the modification. *In re Fritch*, 23 USPQ 1783 (Fed. Cir. 1992).

In addition, unexpected properties must always be considered in the determination of obviousness. A compound's structure and properties are inseparable so that unexpected properties are part of the subject matter as a whole. *In re Papesch*, 315 F.2d 381, 391, 137 USPQ 43, 51 (CCPA 1963).

The instant claims

Instant claim 13 is ultimately dependent on claim 1. As amended herein, claim 1 is directed to a pharmaceutical composition, containing formoterol, or a derivative thereof, in a pharmacologically suitable fluid, wherein the composition is stable during long term storage, the fluid contains water, and the composition is formulated at a concentration suitable for direct administration to a subject in need thereof.

Claims 13-17, 22-26, 30-34, 39-43, 50-53, 55, 56, 58, 80-87 and 97-99 recite that the composition has the recited buffer concentration, ionic strength, formoterol free base concentration, pH, ipratropium bromide concentration, or triotropium concentration.

Claims 65-67, 92 and 93 are directed to combinations of the pharmaceutical composition of claim 1 formulated for single dosage administration and a vial. Claims 71-73 are directed to articles of manufacture containing the compositions of claims 1, 53 and 58, respectively.

The teachings of Hochrainer *et al.*

"Active Substance Concentrate"

Hochrainer *et al.* teaches an "active substance concentrate" containing formoterol in the form of its free base or in the form of one of the pharmacologically acceptable salts or addition products (adducts) thereof as the active substance. This "active substance concentrate" is taught as a "highly concentrated" solution or suspension (*i.e.*, greater than 10 mg/mL, preferably 75 to 500 mg/mL) that is stable for a period of several months, possibly up to

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several years without any deterioration in the pharmaceutical quality (see, *e.g.*, column 1, lines 55-61; column 2, lines 4-7; and claim 1).

Hochrainer *et al.* teaches that it is the high concentration that allows for the stability of the concentrate. The cited reference does not teach or suggest stable, aqueous compositions containing formoterol formulated at a concentration for direct administration to a subject in need thereof, as required by the instantly-claimed compositions.

The "highly concentrated" "active substance concentrate" of the reference is not suitable for direct administration to a subject in need thereof. See, *e.g.*, column 2, lines 1-4:

The term "highly concentrated" means a concentration of the active substance which is usually too high to enable the corresponding solution or suspension to be used therapeutically for inhalation without being diluted.

See also, *e.g.*, column 1, lines 47-52:

The active substance concentrate according to the invention may be converted, by diluting with a pharmacologically acceptable liquid which optionally contains pharmaceutical adjuvants and additives, into a pharmaceutical preparation (aerosol formulation) which is converted by means of a nebulizer into an inhalable aerosol.

See also, *e.g.*, column 4, lines 9-13:

The active substance concentrate according to the invention is not usually suitable as such for direct medicinal use, particularly for inhalation. As already explained, use of the active substance concentrate comprises converting it into a pharmaceutical preparation (aerosol formulation).

Thus, the "active substance concentrate" of Hochrainer *et al.* is merely a means for the storage of highly concentrated solutions of formoterol, and is not formulated at a concentration for direct administration to a subject in need thereof.

"Pharmaceutical Preparation"

Hochrainer *et al.* teaches that the "active substance concentrate" is converted to a "pharmaceutical preparation" prior to administration to a patient. See, *e.g.*, column 1, lines 47-53 and columns 4-5. The reference does not teach or suggest that the "pharmaceutical preparation" is stable during long term storage. As described in detail below, the reference teaches that such formoterol compositions are not stable during long term storage, and thus teaches away from the subject matter of the instant claims.

The "pharmaceutical preparation" of Hochrainer *et al.* is taught for administration to a patient. See, *e.g.*, column 4, lines 13-18:

The term "pharmaceutical preparation" denotes a formulation of a pharmaceutical substance suitable for inhalation wherein a pharmaceutical substance or mixture of substances can be administered in the required and/or recommended concentration.

The reference also teaches methods for administration of the "pharmaceutical preparation" to a patient in need thereof (see, *e.g.*, columns 4-5). However, the reference does not teach or suggest that the "pharmaceutical preparation" is stable during long term storage. As described in detail below, Hochrainer *et al.* teaches away from the subject matter of the instant claims.

Hochrainer *et al.* further distinguishes the "active substance concentrate" taught therein from a "pharmaceutical preparation" at column 5, lines 16-19:

Neither the active substance concentrate suitable for storage according to the invention nor the pharmaceutical preparation for administration obtained by dilution contains a propellant.

Differences from the instant claims

Hochrainer *et al.* teaches a highly concentrated solution or suspension of formoterol "active substance concentrate" that is suitable for storage, but is not suitable for direct administration to a subject in need thereof. The reference teaches that the formoterol "active substance concentrate" is converted to a "pharmaceutical preparation" which is administered to a patient. The reference

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does not teach or suggest that the "pharmaceutical preparation" is stable during long term storage.

In contrast, the pharmaceutical compositions containing formoterol of the instant claims are formulated in a pharmacologically suitable fluid, where the composition is stable during long term storage, the fluid contains water, and the composition is formulated at a concentration suitable for direct administration to a subject in need thereof. Hochrainer *et al.* does not teach or suggest these compositions.

A prior art reference must be considered in its entirety, *i.e.*, as a whole, including portions that would lead away from the claimed subject matter. See, *e.g.*, *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), cert. denied, 469 U.S. 851 (1984). A *prima facie* case of obviousness may be rebutted by showing that the art, in any material respect, teaches away from the claimed invention. See, *e.g.*, *In re Geisler*, 116 F.3d 1465, 1471, 43 USPQ2d 1362, 1366 (Fed. Cir. 1997).

Hochrainer *et al.* teaches an "active substance concentrate" that must be diluted prior to administration to a subject in need thereof. The reference neither teaches nor suggests that the "pharmaceutical preparation" resulting from dilution of the "active substance concentrate" is stable during long term storage. To the contrary, the reference teaches that:

In the past it has been found that liquid aerosol formulations of formoterol are not suitable for use in inhalers intended for ambulatory inhalation treatment since *formoterol cannot be stored in a sufficiently stable manner in solution to guarantee the pharmaceutical quality of the formulation over lengthy periods of time.* (emphasis added)

See, column 1, lines 30-35 of the reference.


Thus, Hochrainer *et al.* teaches away from the claimed subject matter. Therefore, the instant claims cannot be *prima facie* obvious over the teachings of Hochrainer *et al.*

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In view of the above remarks, reconsideration and allowance of the application are respectfully requested.

Respectfully submitted,
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